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Trends in the treatment of risk factors for stroke in a Czech stroke unit

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Abstract: The goal of this study is to evaluate therapeutic trends for several diseases that represent risk factors for stroke. The relative frequency of therapy with compounds that influence the risk factors for stroke was monitored in a group of 3,290 patients who were hospitalised in the Stroke Unit at the University Hospital in Hradec Kralove between 2005 and 2012. For most drugs monitored, the reasons for the significant decrease or increase in use were causes other than the reduction of stroke risk. Despite this finding, the majority of statistically significant changes had, according to review of comparative studies, a positive effect on prevention of stroke. Motivation to change treatment of stroke risk factors, such as hypertension, diabetes mellitus and hypercholesterolemia, was mainly aimed at sufficient disease management with a minimum of adverse effects. On the other hand, optimization of stroke recurrence and economic factors were motivations to treatment changes in prevention with antiplatelets. Antidiabetics were associated with an increase in metformin use and reduction in insulin use. For antihypertensives, the most significant reduction was associated with the use of diuretics, although calcium channel blockers and beta-blockers are also less used. Additionally, the use of the ACE inhibitor ramipril increased

Keywords: trends in the treatment, risk factors, cerebrovascular accidents, stroke

1 Introduction

Most treatable risk factors are common in cerebrovascular and coronary atherosclerosis [1, 2]. The main risk factors include hypertension, diabetes mellitus, dyslipidaemia and smoking. The risk of stroke increases with a combination of these factors [3]. Diabetes mellitus significantly increases the risk of an ischaemic cerebrovascular accident [4-6]. Intensive control of glycaemia after stroke, however, does not improve the prognosis; in fact, it increases the risk of hypoglycaemia. The "United Kingdom Glucose Insulin in Stroke" study even demonstrated an insignificantly higher mortality rate in the group with intensive glycaemia control [7]. An increased cholesterol level is a significant risk factor for stroke [8], and a similar effect is associated with triglyceride levels [9]. Various cholesterol-lowering medications influence the risk of cerebrovascular events to varying degrees [10]. Statins reduce the risk of stroke [11], but when acutely administered in high doses, they can positively influence its consequences. Apart from reducing cholesterol levels, statins also increase the level of endothelial nitric oxide synthetase, which controls the tension of the endothelium and laminar flow. They also increase the expression of endogenous tissue-type plasminogen activator, have antithrombotic effects, improve collateral circulation and reduce inflammatory mediators [12].

2 Materials and methods

2.1 Participants

In a retrospective study of 3,290 patients who were hospitalised in the Stroke Unit at the University Hospital in Hradec Králové (UHHK), we monitored the relative frequency of use over time of six anti-diabetic drugs, two types of statins, 28 antihypertensives and four types of antiplatelet drugs (Table 1) from 2005 to 2012. All patients were admitted for an acute cerebrovascular event. The

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Table 1: Drugs monitored in this study that had a statistically significant increase or decrease in use between 2005 and 2012

Anti-diabetic drugs	glibenclamide, gliclazide, glimepiride, insulin ▼**, metformin ▲*, repaglinide
Statins	atorvastatin ▲*, simvastatin ▼**
Antihypertensives	
ACE inhibitors	captopril, cilazapril, enalapril ▼**, perindopril, ramipril ▲*, trandolapril
Angiotensin II receptor antagonists	losartan, telmisartan
Calcium channel blockers	amlodipine ▼**, diltiazem ▼*, felodipine, nifedipine, nitrendipine, verapamil
Alpha blockers	doxazosin, terazosin ▼*, urapidil
Beta blockers	acebutolol, atenolol, betaxolol, metoprolol
Diuretics	amiloride ▼**, furosemide, hydrochlorothiazide ▼**, indapamide, spironolactone
Centrally acting	methyldopa, rilmenidine
Antiplatelet drugs	aspirin, aspirin + dipyridamol ▼**, clopidogrel ▼**, ticlopidin ▼**

▲ indicates an increasing trend, and ▼ indicates a decreasing trend. * 5% significance level and ** 1% significance level.

drugs used as part of long-term medication taken by the patients before the admission to the Stroke Unit were evaluated. The sample included 46.1 % of women and 53.9 % of men. The mean age was 68.7 ± 14.4 years.

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent has been obtained from all individuals included in this study.

2.2 Statistical methods

Linear regression was used to assess the significance of the observed trends in the use of individual drugs. The values that were considered significant at the 5% significance level, indicating an increasing or decreasing trend in the relative frequencies of administered substances, are discussed, and possible causes are explored.

3 Results

A statistically significant decrease in the relative frequency of use occurred for antiplatelet medications including dipyridamole, clopidogrel and ticlopidine (Fig. 1, Tab. 1). In some patients, these drugs were prescribed for secondary prevention of ischemic heart disease (IHD) and thus they also provided primary prevention of stroke, while in other patients, antiplatelets were prescribed mainly for primary or secondary stroke prevention. An increase in metformin use and a decrease in insulin use occurred among the anti-diabetic drugs (Fig. 2, Tab. 1). Antidiabetics were prescribed to treat diabetes as a stroke risk factor. Therefore, they are to be considered as primary prevention modality. Among the antihypertensives, ramipril was the only drug with a significant increase, whereas a decline occurred in the use of diuretic drugs including amiloride and hydrochlorothiazide, calcium channel blockers including amlodipine and diltiazem, and ACE inhibitors including enalapril and the alpha-blocker terazosin (Fig. 3, Tab. 1). Similar to antidiabetics, antihypertensives were prescribed for primary stroke prevention. In the group of drugs reducing cholesterol levels, the frequency of atorvastatin administration increased at the expense of simvastatin (Fig. 4, Tab. 1). Cholesterol-lowering agents as well as ***antidiabetics*** were prescribed

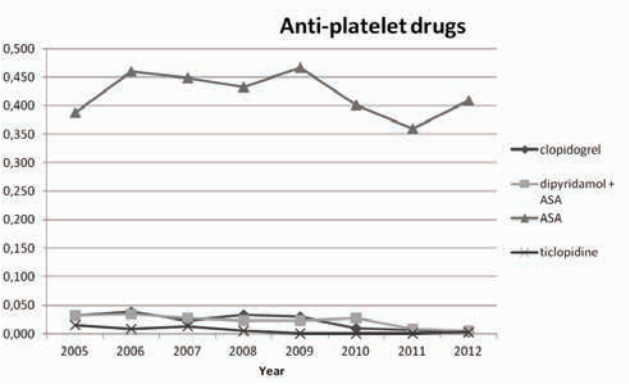

Figure 1: The predominant position of acetylsalicylic acid (ASA) among antiplatelet drugs is connected with a significant decrease in use of all other antiplatelet agents. This trend was caused by changes in guidelines for an antiplatelet therapy of cerebrovascular diseases at the beginning of monitored period.

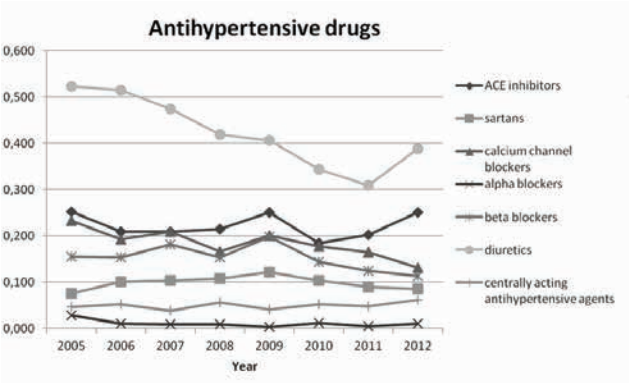

Figure 3: In the treatment of high blood pressure we observed a decrease in use of enalapril and an increase in use of ramipril in a class of ACE inhibitors. In the class of ACE inhibitors in total there was no statistically significant trend. In class of angiotensin II receptor antagonists (losartan a telmisartan) we did not detect any changes in use of individual drugs nor in total. The share of calcium channel blockers was decreasing in monitored period, most distinctly in case of amlodipine and diltiazem. The use of alpha blockers was decreased in total, in this class there is a statistically significant decrease of terazosin. We observed no significant changes in the group of beta blockers as well as in the group of centrally acting antihypertensives. In class of diuretics a decrease of amiloride and hydrochlorothiazide occurred, the share of this group was decreased in total.

for primary prevention of stroke and IHD in patients in whom dietary measures failed.

4 Discussion

Diabetes mellitus is a risk factor for recurrent, mainly lacunar strokes [13]. Despite the positive effects of good compensation of diabetes on reduction of microvascular complications, clinical studies with aggressive reduction

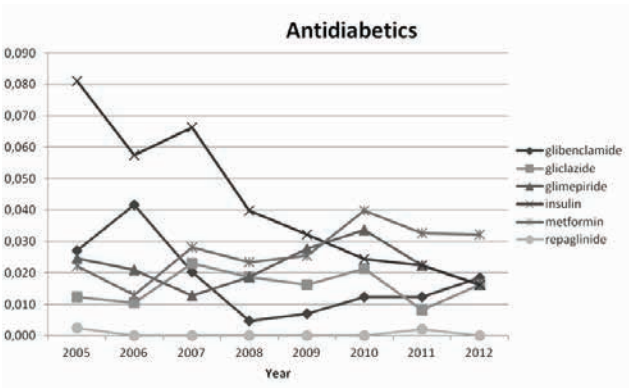

Figure 2: Antidiabetics were associated with a decrease in insulin significant at the 1% significance level, whereas an increase in metformin use was significant at the 5% significance level.

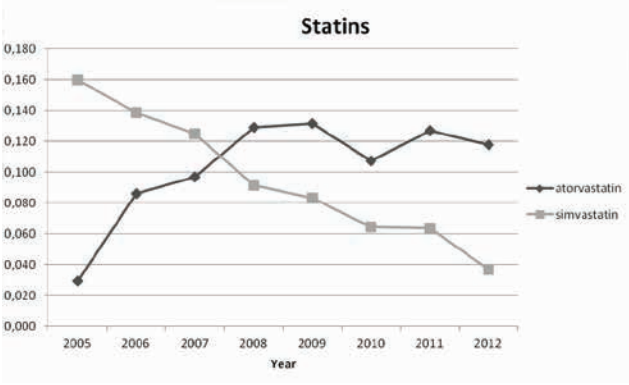

Figure 4: An increase in atorvastatin use (at the 5% significance level) and a decrease in simvastatin use (at the 1% significance level) occurred in the treatment of hypercholesterolemia.

of glycaemia did not prove such approach successful [14]. On the other hand, aggressive reduction of blood pressure and low-density lipoprotein (LDL) cholesterol levels in diabetics leads to important reduction in risk of cerebrovascular events [15, 16]. The significant drop in the number of diabetic patients treated with insulin agrees with the finding that insulin, compared to oral anti-diabetic drugs, has no positive effects on the width of the carotid wall or on vascular function [17]. And the arterial wall thickness of the carotid artery, particularly the intima-media thickness, is an important predictive parameter for ischemic stroke and it can be reliably measured by ultrasound [18]. The anti-sclerotic effect of metformin has been demonstrated [19] and is more significant than the effect of gliclazide or glibenclamide [20], which explains the significant increase in patients treated with metformin (Fig. 2, Tab. 1). Furthermore, therapy with metformin is associated with lower mortality and less cardiovascular risks than therapy with glimepiride or glibenclamide [21]. Metformin is an activator of adenosine 5'-monophosphate-activated protein kinase (AMPK), and if it is administered in experimental cerebral ischemia, it increases

the extent of injury. However, when it was administered chronically before stroke, it had a neuroprotective effect in both experiments and clinical studies [22]. Metformin has been found to support neurogenesis and improve spatial memory [23, 24]. An insignificant decrease in patients treated with glibenclamide was observed, which corresponds with the finding that glibenclamide is associated with a greater risk of complications, such as arrhythmia and ischaemic complications, than glimepiride and gliclazide [25].

Metaanalyses provided evidence that increased LDL levels are associated with increased risk of stroke. Reduction of LDL levels is the main aim of dyslipidemia management after stroke. Each 1 mmol/L reduction of LDL levels is associated with risk reduction of 21 % [26]. In the case of hydroxymethylglutaryl coenzyme A reductase inhibitors (i.e., statins), significantly less negative effects of stroke were demonstrated with atorvastatin than with simvastatin [27]. In the IDEAL study, major cardiovascular events (myocardial infarction and ischaemic cerebrovascular accidents [28]) occurred significantly less often in the group given atorvastatin. Atorvastatin, in comparison with simvastatin, also offers better control of hypercholesterolemia [29]. This fact corresponds with the demonstrated trend toward decreasing the use of simvastatin and the simultaneous increase in the use of atorvastatin for the treatment of hypercholesterolemia in the current group of patients (Fig. 4, Tab. 1).

Studies show a linear correlation between stroke risk reduction and blood pressure. A prospective study showed that every 10 mm Hg reduction of blood pressure in primary prevention reduces the risk of stroke by one third [30]. In addition, patients with pre-existing hypertension have 25% higher risk of stroke than patients without hypertension [31, 32]. In acute phase of cerebrovascular accident numerous prognostic scoring systems are used to predict clinical outcome – systolic or mean arterial blood pressure on admission is typically a very important component of these systems [33]. Antihypertensives comprise a large group of monitored drugs as well as the group whereby the greatest number of new products occurs. A significant increase in ramipril administration was observed (Fig. 3, Tab. 1). In the HOPE study, this drug decreased the relative risk of stroke by 32% and the risk of death following CVA by 61% [34]. A significant drop in use was observed for diuretics such as hydrochlorothiazide and amiloride. Amiloride is associated with the risk of hyperkalaemia and acidosis. Although it has preventive effects against stroke in animal models, human studies have not shown evidence to support this effect [35]. Although hydrochlorothiazide is the most widely used antihypertensive in the world, it has demonstrated lower efficacy than most other antihypertensive drugs, and it is not recommended as a first-choice drug. Furthermore, there is no evidence that hydrochlorothiazide reduces the risk of stroke [36]. However, a significant decrease in the administration of amlodipine (a calcium channel blocker) was observed, even though according to meta-analyses, it provides greater protection against stroke than the other antihypertensive medications that were monitored [37]. Similarly, diltiazem (a calcium channel blocker) decreases the risk of stroke by 25% in comparison with diuretics and betablockers; despite this, a significant decrease in its administration was observed [38]. In the case of the ACE inhibitor enalapril, there is no evidence from human studies available to show that it has a protective effect against stroke. Regarding terazosin administered to patients with hypertension with benign prostate hyperplasia, the reason for the decrease appears to be pharmaco-economic [39]. The greater number of antihypertensives that had a significant declining trend in use for therapy among patients with stroke, compared to other antihypertensives, is due to the small increase in the administration of a large number of various types of new antihypertensives (Fig. 3, Tab. 1). It is still being discussed, whether specific groups of antihypertensives are more effective in primary and secondary prevention of stroke than others. The blood pressure reduction itself is probably the main mechanism of action. Current recommendations do not prefer any specific group of antihypertensives. The choice of antihypertensives in some subgroups of patients with co-morbidities is defined by concurrent treatment of the co-morbidity [40].

The significant drop in administration of all groups of antiplatelet drugs, with the exception of acetylsalicylic acid, was clearly caused by a recommendation by the committee of the cerebrovascular section of the Czech Neurological Society, which prefers a 100 – 150 mg dose of acetylsalicylic acid as the drug of first choice (Fig. 1, Tab. 1).

No significant trends were observed in the use of the anticoagulants.

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References

[1] Mannami T, Baba S, Ogata J. Strong and significant relationships between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city: the Suita Study, Arch.Intern. Med., 2000, 160, 2297-2303

[2] Wilson PW, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis, N. Engl. J. Med., 1997, 337, 516-522

[3] Harmsen P, Lappas G, Rosengren A, Wilhelmsen L. Long-term risk factors for stroke: twenty-eight years of follow-up of 7457 middle-aged men in Göteborg, Sweden, Stroke, 2006, 37, 1663-1667

[4] Arvanitakis Z, Schneider JA, Wilson RS, Li Y, Arnold SE, Wang Z, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons, Neurology, 2006, 67, 1960-1965

[5] Janghorbani M, Hu FB, Willett WC, Li TY, Manson JE, Logroscino G, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study, Diabetes Care, 2007, 30, 1730-1735

[6] Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke, Lancet Neurol., 2012, 11, 261-271

[7] Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK), Lancet Neurol., 2007, 6, 397-406

[8] Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr., Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups, Neurology, 2004, 63, 1868-1875

[9] Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population, JAMA, 2008, 300, 2142-2152

[10] Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials, Arch. Intern. Med., 2003, 163, 669-676

[11] Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention, Lancet Neurol., 2009, 8, 453-463

[12] Moonis M. High-dose statins should be used in all acute ischemic strokes, Stroke, 2012, 43, 1992-1993

[13] Mast H, Thompson JL, Lee SH, et al. Hypertension and diabetes mellitus as determinants of multiple lacunar infarcts. Stroke, 1995, 26, 30-33

[14] Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and theAmerican Heart Association. Circulation, 2009, 119, 351-357

[15] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ, 1998, 317, 703-713

[16] Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet, 2004, 364, 685-696

[17] Joya-Galeana J, Fernandez M, Cervera A, Reyna S, Ghosh S, Triplitt C, et al. Effects of insulin and oral anti-diabetic agents on glucose metabolism, vascular dysfunction and skeletal muscle inflammation in type 2 diabetic subjects, Diabetes Metab. Res. Rev., 2011, 27, 373-382

[18] Farkas S, Molnár S, Nagy K, Hortobágyi T, Csiba L. Comparative in vivo and in vitro postmortem ultrasound assessment of intima-media thickness with additional histological analysis in human carotid arteries. In: Bartels E, Bartels S, Poppert H. New trends in neurosonology and cerebral hemodynamics – an update. Perspectives in Medicine, 2012, 1, 170-176

[19] Scarpello JH, Howlett HC. Metformin therapy and clinical uses, Diab.Vasc. Dis. Res., 2008, 5, 157-167

[20] Katakami N, Yamasaki Y, Hayaishi-Okano R, Ohtoshi K, Kaneto H, Matsuhisa M, et al. Metformin or gliclazide, rather than glibenclamide, attenuate progression of carotid intima-media thickness in subjects with type 2 diabetes, Diabetologia, 2004, 47, 1906-1913

[21] Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study, Eur. Heart. J., 2011, 32, 1900-1908

[22] Li J, Benashski SE, Venna VR, McCullough LD. Effects of metformin in experimental stroke, Stroke, 2010, 41, 2645-52

[23] Wang J, Gallagher D, DeVito LM, Cancino GI, Tsui D, He L, et al. Metformin activates an atypical PKC-CBP pathway to promote neurogenesis and enhance spatial memory formation, Cell Stem Cell, 2012, 11, 23-35

[24] Potts MB, Lim DA. An old drug for new ideas: Metformin promotes adult neurogenesis and spatial memory formation, Cell Stem Cell, 2012, 11, 5-6

[25] Zeller M, Danchin N, Simon D, Vahanian A, Lorgis L, Cottin Y, et al. Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction, J. Clin. Endocrinol. Metab., 2010, 95, 4993-5002

[26] Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol., 2009, 8, 453-463

[27] Lampl Y, Lorberboym M, Gilad R, Vysberg I, Tikozky A, Sadeh M, et al. Early outcome of acute ischemic stroke in hyperlipidemic patients under atorvastatin versus simvastatin, Clin. Neuropharmacol., 2010, 33, 129-134

[28] Scheen AJ. The IDEAL study comparing simvastatin 20-40 mg versus atorvastatin 80 mg for secondary prevention after myocardial infarction: between two ideas of the ideal, Rev. Med. Liege, 2006, 61, 53-59

[29] Karalis DG, Ross AM, Vacari RM, Zarren H, Scott R. Comparison of efficacy and safety of atorvastatin and simvastatin in

patients with dyslipidemia with and without coronary heart disease, Am. J. Cardiol., 2002, 89, 667-671
[30] Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke, 2004, 35, 776-785
[31] Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. Stroke, 2003, 34, 2741-2748
[32] Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA, 2011, 305, 913-922
[33] Szepesi R, Széll IK, Hortobágyi T, Kardos L, Nagy K, Lánczi IL, et al. New prognostic score for the prediction of 30-day outcome in spontaneous supratentorial cerebral haemorrhage. Biomed Res. Int., 2015, article ID 961085, doi: 10.1155/2015/961085
[34] Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangoonwala B, et al. Use of ramipril in preventing stroke: double blind randomised trial, BMJ, 2002, 324, 699-702
[35] Sepehrdad R, Chander PN, Oruene A, Rosenfeld L, Levine S, Stier CT Jr. Amiloride reduces stroke and renalinjury in stroke-prone hypertensive rats, Am. J. Hypertens., 2003, 16, 312-318
[36] Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials, J. Am. Coll.Cardiol., 2011, 57, 590-600
[37] Wang J-G, Li Y, Franklin SS, Safar M. Prevention of stroke and myocardial infarction by amlodipine and angiotensin receptor blockers. A quantitative overview, Hypertension, 2007, 50, 181-188
[38] Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L, Lanke J, et al. Influence of age, sex and blood pressure on the principal endpoints of the Nordic Diltiazem (NORDIL) Study, J.Hypertens., 2002, 20, 1231-1237
[39] Ohsfeldt RL, Kreder KJ, Klein RW, Chrischilles EA. Cost-effectiveness of tamsulosin, doxazosin, and terazosin in the treatment of benign prostatic hyperplasia, J.Manag.Care. Pharm., 2004, 10, 412-422
[40] Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA, 2003, 289, 2560-2572